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(54) Title: METHOD OF TREATMENT AND COMPOSITIONS THEREFOR

(57) Abstract

Method of selectively removing tissue material from a human or animal body comprising administering to a selected region of body tissue a compound which is highly absorbent of infrared radiation of wavelength 750 to 860 nm, and irradiating the region with corresponding infrared radiation at a power sufficient to cause thermal vaporization of the tissue material to which the compound has been administered, but insufficient to cause vaporization of tissue material to which the compound has not been administered. This enables the selective ablation of unhealthy tissue whilst leaving healthy tissue undamaged.

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Method of treatment and compositions therefor

The present invention relates to a method of selectively removing tissue material from a human or animal body, and to a compound and composition for use in such a method.

The use of lasers in medicine for the destruction and removal of tissue is well known. Thus, lasers have been used to remove malignant tumours by thermal vaporization of the tumour tissue. Similarly, such thermal vaporization induced by laser radiation has been utilized in the removal or recanalisation of arterial lumens.

Such known methods of laser treatment are, however, problematic insofar as they are unselective in respect of the tissue that is destroyed by the laser light. Generally speaking, high powers of irradiation are required to cause the vaporization of tissue material. Such high power radiation will destroy healthy as well as unhealthy tissue with which it comes into contact. Some selectivity can be introduced in surface applications by focusing the laser radiation onto the area of interest or non-surface applications by introducing the laser radiation through an optical fibre. However, locating unhealthy tissue is difficult and, once located, ablation of the unhealthy tissue requires high power levels. Furthermore, there is no selectivity between healthy and unhealthy tissue material. This is a problem at the boundary between healthy and unhealthy tissue and especially when the laser radiation has to pass through healthy tissue material before reaching the unhealthy tissue material.

According to one aspect, the present invention provides a method of selectively removing tissue material from a human or animal body, which method

comprises:

(a) administering substantially to a selected region only of body tissue a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm; and

(b) irradiating said region with infra red laser radiation of wavelength 750 to 860nm at a power sufficient to cause thermal vaporization of the tissue material to which said compound has been administered, but insufficient to cause substantial vaporization of tissue material to which said compound has not been administered.

There is also provided the use of a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm in the manufacture of an agent for use in such a method.

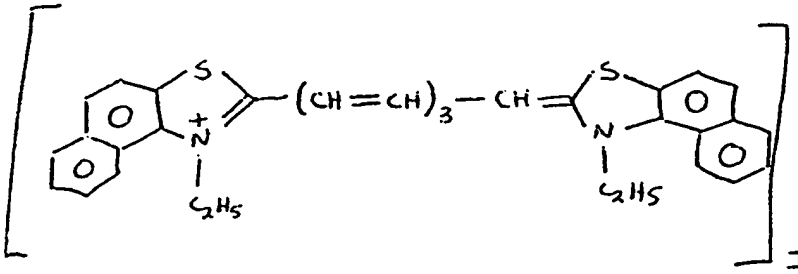
The administering of a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm to the tissue of interest significantly increases the absorption of infra red radiation into that particular tissue. However, most untreated body tissue has a low absorption coefficient for such infra red radiation. The following table exemplifies the decrease in absorption coefficient (μa) in untreated rat liver tissue around 800nm:

Table

Laser	Wavelength (nm)	μa (cm^{-1})
Ar	488	12.2
He-Ne	633	6.5
Ga-As	800	5.7
Nd:YAG	1064	5.9
Nd:YAG	1320	6.6
Ho	2100	27.2

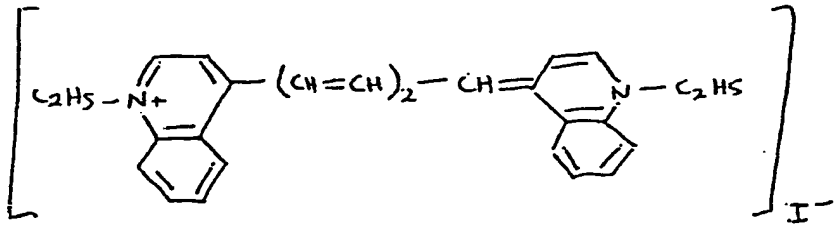
Thus, on passing such infra red radiation of a given power into treated and untreated tissue, there will be a significantly greater absorption of infra red radiation by the treated tissue than by the untreated tissue i.e. normal tissue has a high transmittance of infra red radiation. This allows the power of the laser radiation to be lowered to a level which is sufficient to cause vaporization of the treated tissue material (which has a higher absorption coefficient for infra red radiation) and yet insufficient to cause substantial vaporization of the untreated tissue material. Thus, using the method of the present invention, it is possible to selectively "target" areas/volumes of tissue to be destroyed by irradiation with infra red laser radiation with the target areas underlying other tissue through which the infra-red laser light passes.

The compound which is highly absorbent of such infra red radiation may be any such compound that is soluble in water or "soluble" in serum (by "soluble" in serum it is meant that the compound is capable of binding to serum proteins which may transport it to the appropriate site; such compounds need not be fully water soluble). Suitable compounds are dyes capable of absorbing near infra red radiation such as polymethine dyes which are soluble in water or bind readily to proteins. Examples of suitable polymethine dyes are:



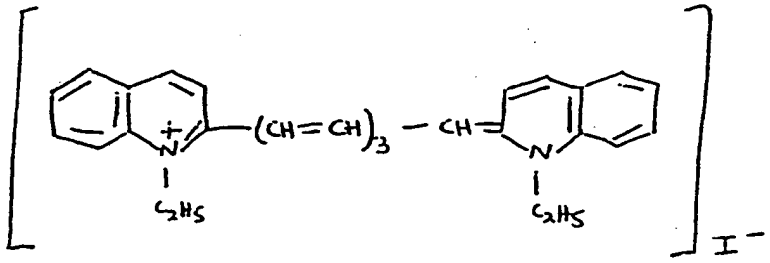
(I)

3,3'-diethyl-2,2'-(4,5,4',5'-dibenzo)-thiatricarbocyanine iodide.



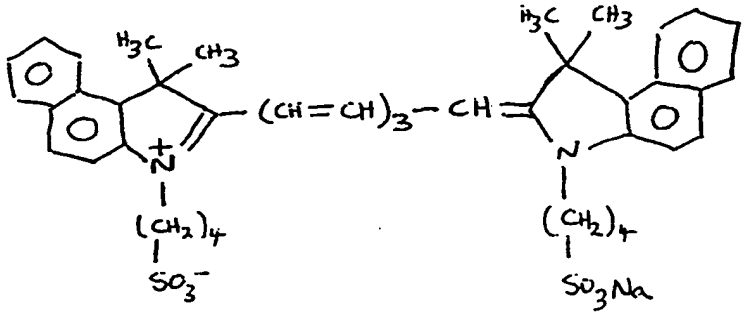
(II)

1,1'-diethyl-4,4'-quinodicarbocyanine iodide.



(III)

1,1'-diethyl-2,2'-quinotricarbocyanine iodide.



(IV)

Indocyanine Green (ICG)

{2-(7-[1,3-dihydro-1,1-dimethyl-3-(1-sulphobutyl)-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulphobutyl)-1H-benz[e]indolium hydroxide inner salt sodium salt]}

Of these compounds, indocyanine green (ICG) or its analogues are particularly suitable, being particularly soluble in water and being generally available. Furthermore, ICG strongly absorbs infra red radiation at wavelengths of 780-820 nm. In particular, ICG is clinically proven, non-toxic and is safe. Such a compound has a strong IR absorbance at 805nm and also fluoresces under IR irradiation.

Fig. 1 shows an absorption spectrum of normal serum containing 5mg/l of ICG; the marked absorption peak at around 805nm is apparent. This coincides with the wavelength region over which normal tissue has its minimum absorbance, as exemplified in the rat liver in the Table above and as shown in the increased reflectance of human skin in this range (see Fig. 2). Such a "window" is advantageous since the peak of absorbance for ICG corresponds to a trough of absorbance for normal body tissue, thus maximizing the ablation of unhealthy tissue whilst minimizing the destruction of healthy tissue.

Suitable compounds will preferably have an absorption coefficient of at least $0.5cm^{-1}$, more preferably 0.5 to 10 cm^{-1} for infra red radiation of wavelength 750 to 860nm.

Other suitable infra red absorbing compounds include chlorophyll and other porphyrin or haeme-containing compounds, or compounds containing a polyene structure, all of which must be capable of strongly absorbing IR radiation of wavelength 750 to 860 nm.

Irradiation may be achieved using any laser operating in this infra red wavelength range. Thus, for example, gas lasers or diode lasers may be used. High power diode lasers are particularly suitable, typically emitting infra red radiation of wavelengths of 780 to 830 nm. Such lasers may typically have a power range of 2 to 3W, and diode lasers are particularly advantageous over gas lasers in that they are inexpensive, robust and

compact.

Typical power levels which will cause destruction of treated tissue whilst leaving untreated tissue substantially unvapourized are 50-1000W/cm^2 depending on the particular tissue the quantity of highly infra-red absorbent compound present in the tissue and the spot diameter. The power level required will, of course, depend to a certain extent on the type of tissue to be ablated, and so certain tissues may require even higher power levels in order to achieve ablation. However, for the method of the present invention, the low power levels required compare exceptionally favourably with typical power levels required to achieve destruction of untreated tissue - e.g. power levels of over 1000 W/cm^2 are required to ablate untreated tissue material from pig aorta, whereas power levels of only approx. 100 W/cm^2 are required to ablate tissue material from pig aorta after immersion for 30 minutes in 25 mg/l ICG in saline, using a laser beam of 3 mm diameter.

The compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm is preferably administered to the tissues by intravenous administration. Although less preferable, administration may also be by the intradermal, subcutaneous or intramuscular route. Thus, selective administration may be achieved utilizing the differential take up of infra red absorbing compounds, e.g. ICG, by different tissues. For example, dyes are known to clear more slowly from cancerous tissue than from normal tissue; arteriosclerotic plaque absorbs dyes more strongly than the intima of the arterial wall.

Furthermore, the compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm may be administered through the medium of a binding agent chosen to bind the compound to the selected region only of body tissue. Thus, according to a further aspect, the present invention provides a method of selectively

removing tissue material from a human or animal body, which method comprises:

(a) administering to said body a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm;

(b) administering to said body or substantially to a selected region of tissue thereof, a substance capable of preferentially binding said compound substantially to a selected region of body tissue, said substance being administered with said compound or before or after said compound has been administered; and

(c) irradiating said region with infra red laser radiation of wavelength 750 to 860nm at a power sufficient to cause vaporization of the tissue material to which said compound is bound, but insufficient to cause substantial vaporization of tissue material to which said compound is not bound.

There is also provided the use of a composition comprising a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm bound to a substance capable of binding said compound substantially to a selected region of body tissue, in the manufacture of an agent for use in such a method. There is also provided the use of a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm in the manufacture of an agent for use in such a method.

This has the advantage that tissue/site specific agents may be used to bind the infra red absorbing compound to the tissue, for example cancerous tissue or atherosclerotic plaque - i.e. this is highly tissue selective.

Thus, for example, monoclonal antibodies may be used as the binding agent to which the infra red absorbing compound becomes attached. Such antibodies may be chosen to attach preferentially or specifically

to the tissue which is to be ablated. Suitable monoclonal antibodies are known for a variety of cancerous tissues and arteriosclerotic plaque.

Thus, there may be used monoclonal antibodies which bind to antigens in cancerous cells, examples of such antigens being CEA (carcino embryonic antigen) and CA 125 (cancer antigen no. 125).

Attachment of the highly infra red absorbent compound to the monoclonal antibody may be achieved via an analogue of the highly infra red (wavelength 750-860nm) absorbent compound, e.g. an analogue of ICG, which reacts directly with the antibody molecule. Alternatively, the highly infra red absorbing compound, e.g ICG, may be bound to a carrier molecule, e.g. human serum albumin, which molecule may be cross-linked to the antibody molecule of interest.

It is particularly preferable to use a bispecific monoclonal antibody as the binding agent. Such a bispecific monoclonal antibody is a hybrid molecule which has one binding site for the cell of the tissue of interest, e.g. a cancer cell or a cell of atheroselerotic tissue, and a second binding site with a different specificity, in the case of the present invention a specificity for the highly infra red absorbent compound, e.g. ICG. Bispecific monoclonal antibodies may be made using the method of Milstein (Milstein, C. Nature 305, 573 (1983)). Thus, for example, bispecific monoclonal antibodies may be prepared by fusing cell lines producing molecules specific for cancer cells or atherosclerotic tissue cells and cell lines producing molecules specific for ICG to produce resultant hybrid antibodies. Use of such bispecific monoclonal antibodies is preferred since they are simple molecules that do not require the presence of cross-linking or other agents which may prove to be antigenic.

Monoclonal antibodies are particularly useful as

binding agents in the removal of blood clots in arteries. Thus, a monoclonal antibody raised against fibrin may be administered followed by administration of the highly infra red (wavelength 750 to 860nm) absorbent compound. The highly infra red absorbent compound, e.g. ICG, will bind to the bound antibody and an infra red laser may be targeted on the thus-labelled fibrin to ablate the blood clot and thereby clear the artery.

Various other binding agents may be used. Thus, for example, low density lipoproteins (LDL) and very low density lipoproteins (VLDL) are particularly suited to binding compounds which are highly absorbent of infra red radiation of wavelength 750 to 860nm, such as ICG, specifically to atherosclerotic plaque tissue. Blood proteins, for example synthetic blood proteins, which identify the early stages of the build-up of atherosclerotic plaque on artery walls may be used. An example of such a synthetic protein which may be used is a peptide named SP-4 of Diatech, Inc. of Boston, Massachusetts, USA. Needless to say, all such agents must be capable of binding to both the infra red absorbing compound and the tissue of interest.

It should be borne in mind that the absorption peak of the infra red absorbing compound will vary with the nature of the substance e.g. the binding substance to which it is bound. Thus, for example, albumin-bound ICG will have an absorption peak at about 805nm. In such circumstances, irradiation with IR radiation at a wavelength of about 805nm will be preferable. It is known that, for example, the ICG absorption spectrum changes when mixed with blood, mainly due to bonding with plasma proteins. ICG dissolved in water shows a peak absorption at 786nm. Binding to collagen produces a slightly different wavelength maximum (see Example 2). Thus, the wavelength of the laser radiation will need to be adjusted to the absorption maximum of the infra-red absorbing substance in its particular environment.

In applying the method of the invention, it is useful to be able to locate the target tissue. Thus, according to another aspect, the invention provides a method of selectively removing tissue material from a human or animal body, which method comprises:

(a) administering substantially to a selected region only of body tissue a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm and capable of emitting fluorescent radiation when irradiated with infra red radiation;

(b) irradiating said region with infra red laser radiation at a power insufficient to cause vaporization of tissue but sufficient to cause the emission of fluorescent radiation from said compound;

(c) aiming the treatment laser by locating fluorescence from said compound; and

(d) irradiating said region with infra red laser radiation of wavelength 750 to 860nm at a power sufficient to cause vaporization of the tissue material to which said compound has been administered, but insufficient to cause substantial vaporization of tissue material to which said compound has not been administered.

Subsequently to step (d), the fluorescent radiation emitted from the tissue material treated in accordance with step (a) may be monitored during treatment in order to determine the extent of tissue removal.

There is also provided the use of a compound or composition which is highly absorbent of infra red radiation of wavelength 750 to 860nm and capable of emitting infra red radiation, in the manufacture of an agent for use in such a method.

This method enables the location of treated tissue and preferably the remote monitoring of the extent of tissue removal. Typically, the laser, e.g. a diode laser, will be operated at a power below that which

would have a therapeutic effect. The laser radiation is directed either as a focused beam or as a beam which is, for example, a few millimetres in diameter onto the tissue to which the infra red absorbing compound has been administered; fluorescent light from the compound, e.g. ICG, is monitored as the laser beam is scanned over the tissue. When treated tissue is in the beam, fluorescent light will be detected. At this point the laser power is increased by an amount sufficient to give a therapeutic effect. Monitoring of the fluorescent emission during treatment allows the extent of tissue destruction to be monitored; when all of the treated tissue has been removed the fluorescent signal will terminate. Whilst it is possible to use two lasers, one to ablate the tissue and the other to cause fluorescence, a particular advantage of this method is that it allows the use of a single laser to both ablate the tissue material and cause fluorescence, i.e. to aim, treat and monitor.

The laser radiation may be delivered to the target area and fluorescence monitored via a body implantable optical fibre.

Such a method has a further significant advantage over UV-based methods which have been used in the prior art. Almost all natural materials fluoresce to some extent when irradiated with UV light. The selectivity of detection is therefore low due to the high fluorescence background from normal tissue. However, infra red fluorescing materials are rare and most natural materials do not fluoresce under infra red irradiation. The use of infra red irradiation therefore gives a much higher contrast and lower noise fluorescence signal.

Suitable compounds which both absorb infra red radiation of wavelength 750-860nm and fluoresce under infra red irradiation are the above-mentioned polymethine dyes, especially ICG, and compounds such as

chlorophyll.

ICG is particularly suitable for use in this method of removing tissue, enabling location of the treated tissue and the monitoring of the extent of removal, especially in combination with a variable output diode laser.

When applying the infra red absorbing substance directly, without the mediation of a binder substance, the substance may be applied by conventional intravenous administration, preferably in an injectable solution at a concentration of 1-100 mg/ml. As mentioned above, although less preferable, administration may alternatively may be by the intradermal, subcutaneous or intramuscular route. In its broadest aspect the present invention provides the use of a compound which is highly absorbent of infra red radiation in the manufacture of an agent for use in a method of selectively removing tissue material from a human or animal body.

When using a binding agent, for example a monoclonal antibody, to bind the compound which is highly absorbent of infra red radiation to the target tissue, the compound may be administered to the body or tissue first and then the binding substance, or vice versa. When bispecific monoclonal antibodies are used, they may be administered to the patient first, by intravenous injection, and then the infra red absorbing compound, e.g. ICG, may be added in a second intravenous injection. Only those antibodies bound to the tumour will bind the infra red absorbing compound. For the sake of convenience, the compound and binder are preferably administered together to the body. Thus, in another aspect, the invention provides a pharmaceutical composition comprising a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm bound to a substance capable of preferentially binding said compound to a selected region of body tissue, together with at least one inert excipient.

The binder substance, e.g. bispecific monoclonal antibodies, may conveniently be administered at a concentration of 10μg/ml to 10mg/ml, for example 1 mg/ml, on its own or in a composition including the highly infra red absorbing compound. Monoclonal antibodies may conveniently be obtained as a freeze-dried powder which is then made up to the required strength with physiological saline.

Administration of the binder substance, e.g. monoclonal antibodies or LDL's, in the presence or absence of the highly infra red absorbent compound, may be conveniently achieved by slow infusion through a vein in an arm or a hand in the case of humans, delivery taking place over a period of several hours. Administration is a delicate procedure and due care has to be taken to try to minimise allergic or immune reactions.

The above possibilities are equally applicable when the infra red absorbing compound is also capable of emitting fluorescent radiation when irradiated with infra red radiation.

The methods according to the present invention are applicable to a wide range of medical procedures in which tissue is to be removed or destroyed. Such procedures include (but are not limited to) oncology, angioplasty, gastrointestinal and urinary tract surgery, neurology and dermatology. Such methods are applicable to the human body and also to the (non-human) animal body.

In the accompanying drawings:

Fig. 1 is a spectrophotometric curve (Absorption vs. Wavelength (nm)) for normal serum containing 5mg/l of "Cardio-Green" (Sterile Indocyanine Green USP).

Fig. 2 is a spectral reflectance plot for human skin (skin reflectance vs. wavelength (μm)).
..... fair-skin individuals

------- heavily-pigmented skin individuals.

Fig. 3 is an absorption spectrum (Absorbance X1000 vs. wavelength (nm) for 0.02% (w/v) rat tail (RT) tendon (Type I) collagen dissolved in 0.1M acetic acid.

Fig. 4 is an absorption spectrum (% Maximum Absorbance vs. Wavelength (nm) for ICG dissolved in 0.1M acetic acid. Spectrum normalized to percent maximum of peak absorbance value.

Fig. 5 is an absorption spectrum (% Maximum Absorbance vs. Wavelength (nm)) for collagen dissolved in acetic acid combined with ICG dissolved in acetic acid (.....); ICG/acetic acid absorption spectrum (+++++) for comparison. Both spectra normalized to their peak values.

The invention will now be illustrated by means of the following non-limiting Examples:

Examples

Example 1: In vitro experiments

An aqueous solution of ICG was prepared to concentration 25mg/litre (this was very pale green in colour).

A 10mm cuvette of ICG was illuminated using laser diode radiation through an 800 nm filter. Fluorescence was observed through a 830 nm optical filter. Fluorescence was observed through the depth of the cell. No excitation radiation was transmitted through the cell.

Human femoral artery segments were defrosted, opened up into flat segments and soaked in concentrated (25mg/5ml) ICG for 1 hour. The samples were then rinsed in saline.

Initially, a collimated laser beam (power = 1 W, diameter = 8 mm, power density = 2 W/cm^2 was used and fluorescence observed as described above.

The beam was then focused onto the sample (200 μm spot size) and significant burning observed at power densities of around a few hundred Watts/cm^2. At these power densities, no burning of tissue was observed for the control sample which had been soaked in saline.

These experiments were repeated at lower ICG concentration of around 25 mg/1; tissue removal for treated tissue occurred for power densities of around 100 W/cm^2. In contrast, a power density at least 10 times greater than this was required to produce similar effects in untreated tissue.

These experiments clearly show ICG is absorbed by artery and that treated artery shows a much higher absorption of laser radiation (by a factor of at least 10) than untreated artery, allowing removal of tissue at low power levels.

Example 2: Variation of absorption maximum

a) ICG and collagen preparation

Dried, Type I collagen from rat tail tendon (Sigma) was dissolved according to the supplier's instructions at room temperature in 0.1M acetic acid to produce a 0.2% (w/v) solution ("collagen/acetic acid"). A 0.02% (w/v) solution of ICG was prepared by dissolving ICG (Sigma) in double distilled water. Then 100 μL of the ICG solution was added to 900 μL of 0.1M acetic acid ("ICG/acetic acid"). The ICG/acetic acid solution was further diluted 1:10 in distilled water for spectral measurements. Samples of the solutions were placed in plastic cuvettes with the appropriate solvent (acetic acid) in a comparison cuvette. Following spectral absorbance measurements of ICG/acetic acid and RT collagen/acetic acid, the collagen solution was divided,

half being added to an equal volume of ICG/acid. Spectral absorption measurements were then made of the combined solution.

b) Spectral measurements

Spectral absorbance measurements were made using a Perkin-Elmer Spectrophotometer (Model 552) with a slit setting of 2nm, a time constant of 0.5 sec, and a scan rate of 120nm/min. Absorbance was measured every 4nm between 400 and 900nm from the plotted absorbance curves and entered into a computer program that allowed the data to be manipulated mathematically and plotted so the various spectra could be normalized.

c) Results

i) Type I collagen

Fig. 3 shows the absorption spectrum of Type I collagen dissolved in 0.1M acetic acid. Absorbance is equal at all wavelengths tested (i.e. the spectrum is "flat") indicating that Type I collagen does not absorb differentially within the 500-900nm band. Absolute absorbance is quite low (4×10^{-4} Absorbance Units) because the collagen solution is relatively dilute which, in turn, is due to the relatively low solubility of Type I RT collagen.

ii) ICG solutions

The absorption spectra of ICG/acetic acid are shown in Fig. 4. The ICG/acetic acid spectrum peak was at 778nm, with a plateau from 716nm to 728nm.

iii) ICG combined with collagen

The absorption spectrum of lagen/acetic acid combined with ICG/acetic ac exhibits two peaks (Fig. 5). The main peak is shifted by 28nm from the ICG/acetic acid peak (i.e. 778 to 806nm). The lower peak of the combined solution at 736nm (93% relative absorbance) does not correspond to a shift of 28nm of the knee of the plateau region of the ICG/acetic acid spectrum (716-728nm). Thus, the combined spectrum shifts toward longer wavelengths.

CLAIMS:

1. The use of a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm in the manufacture of an agent for use in a method of selectively removing tissue material from a human or animal body, which method comprises:

(a) administering substantially to a selected region only of body tissue a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm; and

(b) irradiating said region with infra red laser radiation of wavelength 750 to 860nm at a power sufficient to cause thermal vaporization of the tissue material to which said compound has been administered, but insufficient to cause substantial vaporization of tissue material to which said compound has not been administered.

2. The use as claimed in claim 1, wherein said compound is a compound that is soluble in water or soluble in serum.

3. The use as claimed in claim 1 or claim 2 wherein said compound has an absorption coefficient of at least $0.5cm^{-1}$ for infra red radiation of wavelength 750 to 860nm.

4. The use as claimed in claim 3 wherein said absorption coefficient is 0.5 to $10cm^{-1}$.

5. The use as claimed in any one of the preceding claims wherein said compound has an absorption peak at a wavelength of about 805nm.

6. The use as claimed in claim 5 wherein said region is irradiated with infra red laser radiation of wavelength about 805nm.

7. The use as claimed in any one of the preceding claims, wherein said compound is a polymethine dye.

8. The use as claimed in any one of the preceding claims wherein said compound is (2-(7-[1,3-dihydro-1,1-dimethyl-3-(1-sulphobutyl)-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulphobutyl)-1H-benz[e]indolium hydroxide inner salt sodium salt]) or an analogue thereof.

9. The use as claimed in any one of the preceding claims wherein step (a) is achieved by administering to said body a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm, and administering to said body or substantially to a selected region of tissue thereof, a substance capable of preferentially binding said compound substantially to a selected region of body tissue, said substance being administered with said compound or before or after said compound has been administered.

10. The use as claimed in any one of the preceding claims wherein said compound is capable of emitting fluorescent radiation when irradiated with infra red radiation and wherein the following steps are performed before step (b):

(i) irradiating said region with infra red laser radiation at a power insufficient to cause vaporization of tissue but sufficient to cause the emission of fluorescent radiation from said compound; and

(ii) aiming the treatment laser by locating fluorescence from said compound.

11. The use of a compound or composition which is highly absorbent of infra-red radiation of wavelength 750 to 860nm in the manufacture of an agent for use in a method of selectively removing tissue material from a human or animal body, which method comprises:

(a) administering to said body a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm;

(b) administering to said body or substantially to a selected region of tissue thereof, a substance capable of preferentially binding said compound substantially to a selected region of body tissue, said substance being administered with said compound or before or after said compound has been administered; and

(c) irradiating said region with infra red laser radiation of wavelength 750 to 860nm at a power sufficient to cause vaporization of the tissue material to which said compound is bound, but insufficient to cause substantial vaporization of tissue material to which said compound is not bound.

12. The use as claimed in claim 11, wherein said substance is a monoclonal antibody.

13. The use as claimed in claim 12, wherein said monoclonal antibody is a bispecific monoclonal antibody.

14. The use as claimed in claim 11, wherein said substance is a low density lipoprotein or very low

d nsity lipoprotein.

15. The use as claimed in any one of claims 11 to 14, wherein said compound is a compound that is soluble in water or soluble in serum.

16. The use as claimed in any one of claims 11 to 15, wherein said compound is a polymethine dye.

17. The use as claimed in any one of claims 11 to 16, wherein said compound is {2-(7-[1,3-dihydro-1,1-dimethyl-3-(1-sulphobutyl)-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulphobutyl)-1H-benz[e]indolium hydroxide inner salt sodium salt]} or an analogue thereof.

18. The use of a compound or composition which is highly absorbent of infra red radiation and capable of emitting infra red radiation in the manufacture of an agent for use in a method of selectively removing tissue material from a human or animal body, which method comprises:

(a) administering substantially to a selected region only of body tissue a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm and capable of emitting fluorescent radiation when irradiated with infra red radiation;

(b) irradiating said region with infra red laser radiation at a power insufficient to cause vaporization of tissue but sufficient to cause the emission of fluorescent radiation from said compound;

(c) aiming the treatment laser by locating fluorescence

from said compound; and

(d) irradiating said region with infra red laser radiation of wavelength 750 to 860nm at a power sufficient to cause vaporization of the tissue material to which said compound has been administered, but insufficient to cause substantial vaporization of tissue material to which said compound has not been administered.

19. The use as claimed in claim 18, wherein subsequently to step (d), the fluorescent radiation emitted from the tissue material treated in accordance with step (a) is monitored during treatment in order to determine the extent of tissue removal.

20. The use as claimed in claim 18 or claim 19, wherein said compound is a compound that is soluble in water or soluble in serum.

21. The use as claimed in any one of claims 18 to 20, wherein said compound is a polymethine dye.

22. The use as claimed in any one of claims 18 to 21 wherein said compound is {2-(7-[1,3-dihydro-1,1-dimethyl-3-(1-sulphobutyl)-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulphobutyl)-1H-benz[e]indolium hydroxide inner salt sodium salt]} or an analogue thereof.

23. The use of a compound which is highly absorbent of infra red radiation in the manufacture of an agent for use in a method of selectively removing tissue material from a human or animal body.

24. A pharmaceutical composition comprising a compound which is highly absorbent of infra red radiation of

wavelength 750 to 860nm bound to a substance capable of preferentially binding said compound to a selected region of body tissue, together with at least one inert excipient.

25. A pharmaceutical composition as claimed in claim 24 wherein said compound is capable of emitting fluorescent radiation when irradiated with infra red radiation.

26. A pharmaceutical composition as claimed in claim 24 or claim 25 wherein said compound is {2-(7-[1,3-dihydro-1,1-dimethyl-3-(1-sulphobutyl)-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulphobutyl)-1H-benz[e]indolium hydroxide inner salt sodium salt]} or an analogue thereof.

27. A method of selectively removing tissue material from a human or animal body, which method comprises:

(a) administering substantially to a selected region only of body tissue a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm; and

(b) irradiating said region with infra red laser radiation of wavelength 750 to 860nm at a power sufficient to cause thermal vaporization of the tissue material to which said compound has been administered, but insufficient to cause substantial vaporization of tissue material to which said compound has not been administered.

28. A method of selectively removing tissue material from a human or animal body, which method comprises:

(a) administering to said body a compound which is highly absorbent of infra red radiation of

wavelength 750 to 860nm;

(b) administering to said body or substantially to a selected region of tissue thereof, a substance capable of preferentially binding said compound substantially to a selected region of body tissue, said substance being administered with said compound or before or after said compound has been administered; and

(c) irradiating said region with infra red laser radiation of wavelength 750 to 860nm at a power sufficient to cause vaporization of the tissue material to which said compound is bound, but insufficient to cause substantial vaporization of tissue material to which said compound is not bound.

29. A method of selectively removing tissue material from a human or animal body, which method comprises:

(a) administering substantially to a selected region only of body tissue a compound which is highly absorbent of infra red radiation of wavelength 750 to 860nm and capable of emitting fluorescent radiation when irradiated with infra red radiation;

(b) irradiating said region with infra red laser radiation at a power insufficient to cause vaporization of tissue but sufficient to cause the emission of fluorescent radiation from said compound;

(c) aiming the treatment laser by locating fluorescence from said compound; and

(d) irradiating said region with infra red laser

radiation of wavelength 750 to 860nm at a power sufficient to cause vaporization of the tissue material to which said compound has been administered, but insufficient to cause substantial vaporization of tissue material to which said compound has not been administered.

FIG. 1

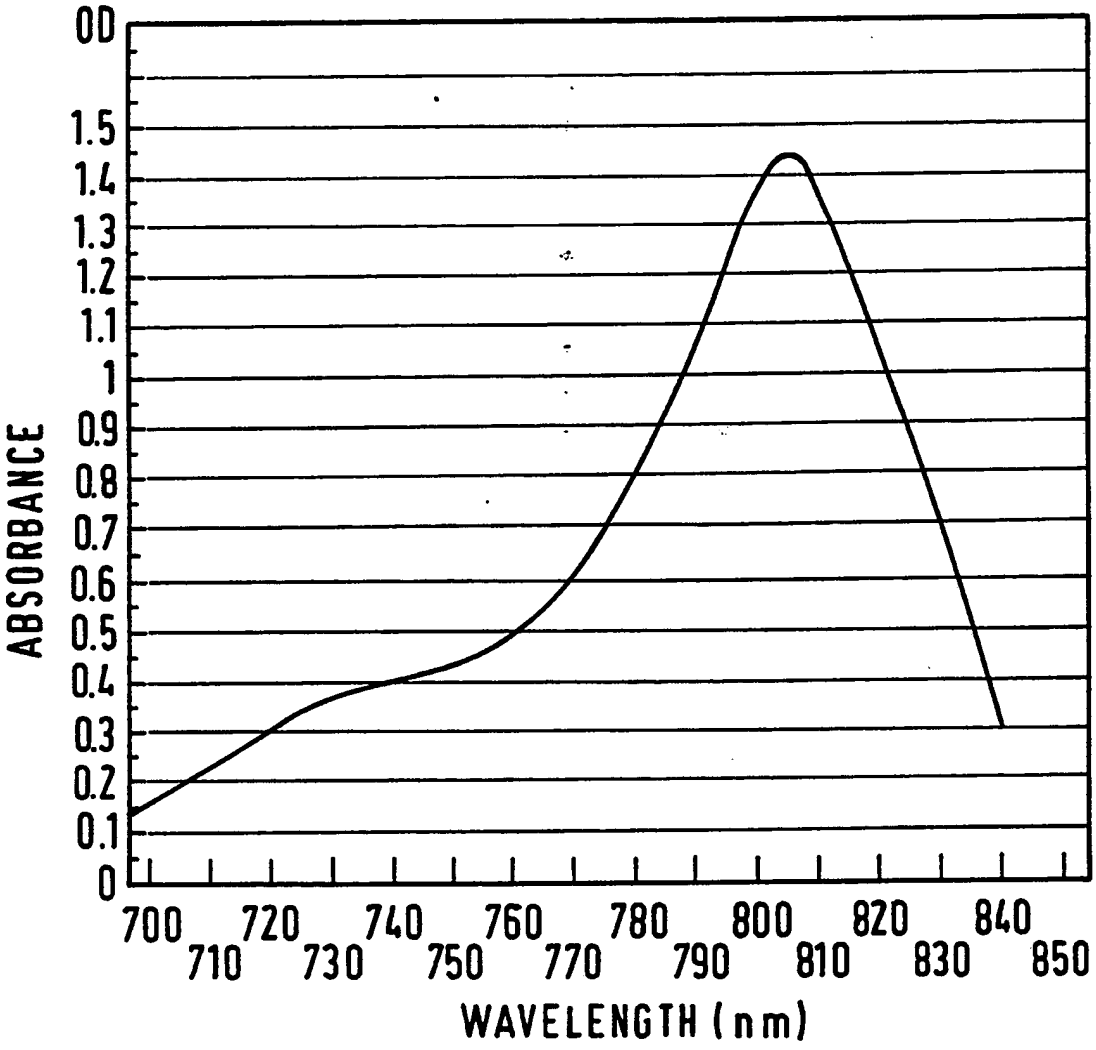

OD
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
ABSORBANCE
700
710
720
730
740
750
760
770
780
790
800
810
820
830
840
850
WAVELENGTH (nm)

FIG. 2

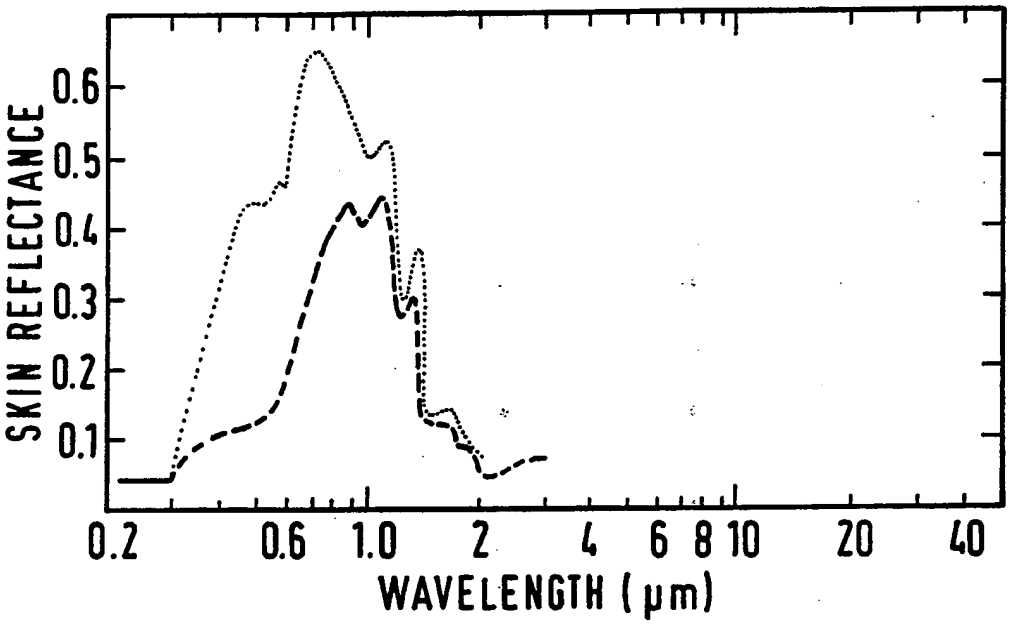

SKIN REFLECTANCE
0.6
0.5
0.4
0.3
0.2
0.1
0.2
0.6
1.0
2
4
6
8
10
20
40
WAVELENGTH (μm)

FIG. 3

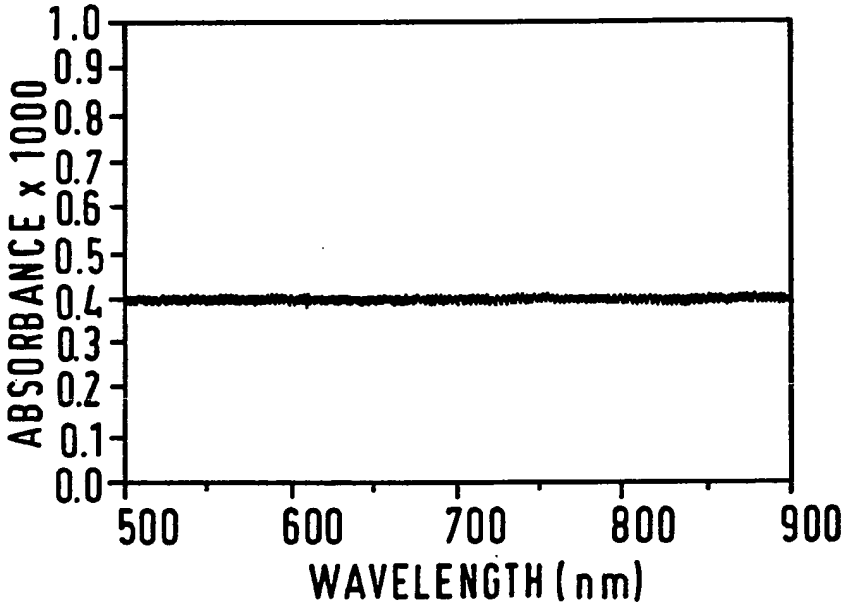

ABSORBANCE x 1000
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
500
600
700
800
900
WAVELENGTH (nm)

FIG. 4

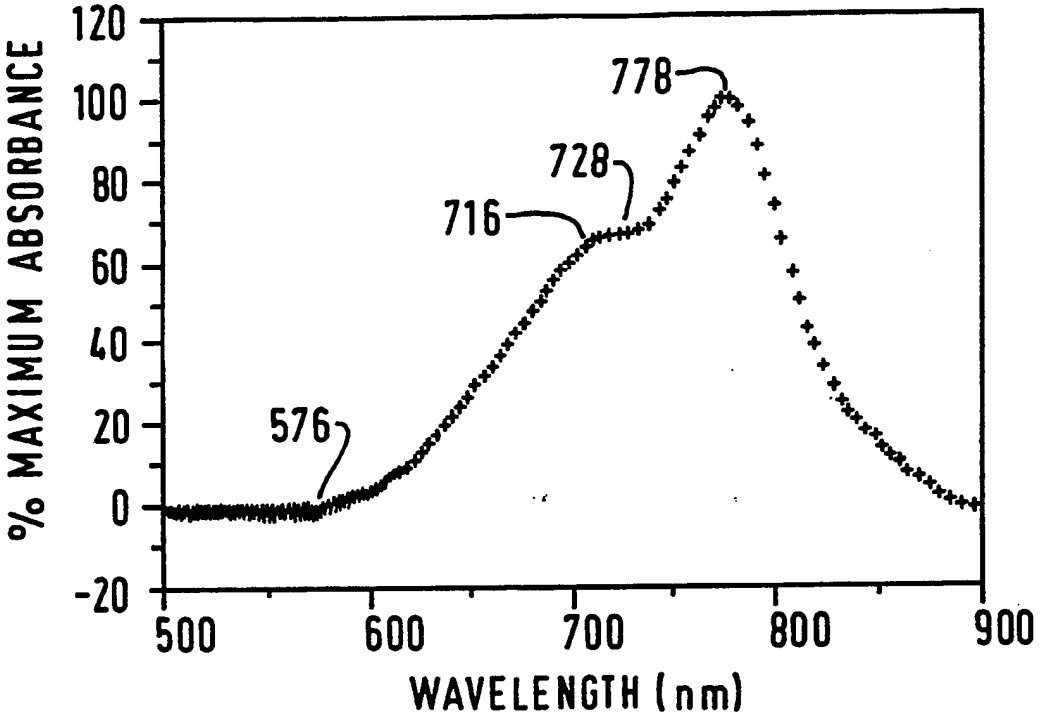
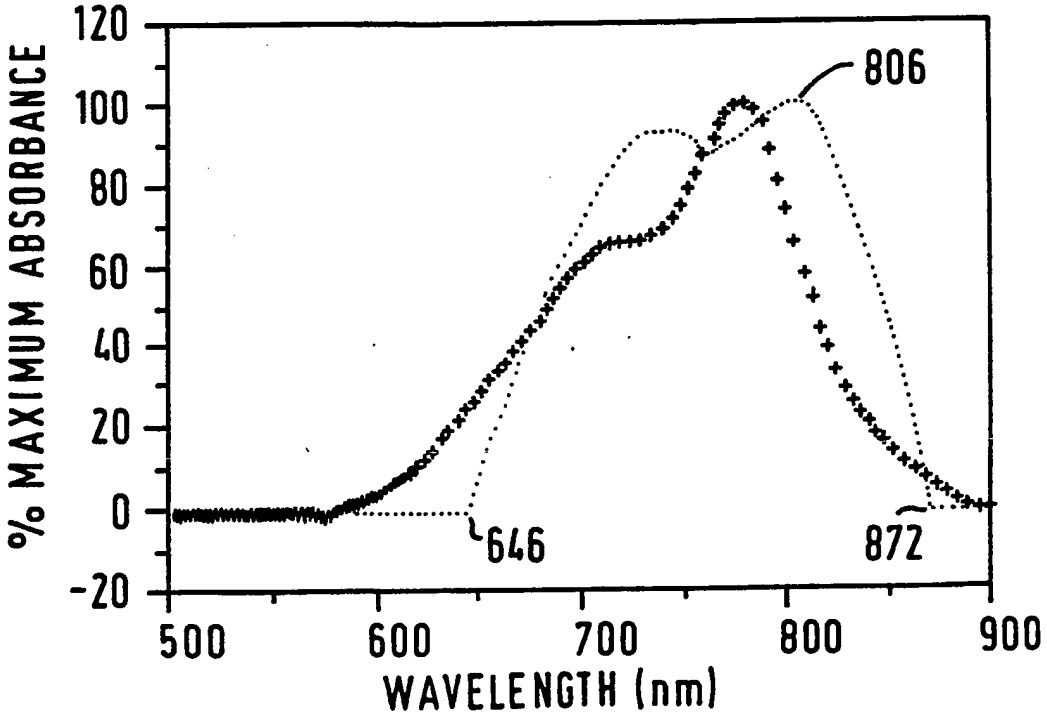

% MAXIMUM ABSORBANCE
120
100
80
60
40
20
0
-20
500
600
700
800
900
WAVELENGTH (nm)
778
728
716
576

FIG. 5


% MAXIMUM ABSORBANCE
120
100
80
60
40
20
0
-20
500
600
700
800
900
WAVELENGTH (nm)
806
646
872